



Feeling the

New scientific discoveries have made the field of migraine research one of the hottest and most exciting for Pfizer's research scientists

When it comes to the diseases that affect our lives, many are unfamiliar with complicated names, like chronic obstructive pulmonary disease, cerebrovascular disease or squamous cell lung carcinoma. However, there is one condition that everyone has heard of, maybe even experienced, but which is still shrouded in mystery, defying the best attempts of scientists to understand its cause and biology. This condition is migraine.

Migraine – and the associated headache – has afflicted humankind for millennia, the first record appearing in Babylonian writings dating from 3,000 BC. Throughout that time, doctors have tried to understand and treat migraine, including early Egyptian physicians, father-of-medicine Hippocrates and second-century Chinese surgeon, Hua T'o, the man credited with the invention of anaesthetic drugs.

Today, migraine attacks disrupt the lives of more than six million people in the UK, three-quarters of whom are women. Every day Britons suffer 190,000 migraine attacks.

In addition to the excruciating pulsing

headache, which can last as long as 72 hours, the symptoms of migraine include visual disturbances and nausea, photophobia and phonophobia (increased sensitivity to light and sound), all of which bring a toll to patients' lives. Migraine also has an economic impact, estimated at £1 billion each year in the UK.

Since the earliest research in the 1940s, scientists have found many new treatments for migraine, bringing relief for patients, and it remains a very active area of scientific research, not least at Pfizer's labs in Sandwich.

So, what is migraine and what exciting new approaches are researchers investigating in the search for new and more effective treatments?

Brain ache

Over the years, scientists have developed many theories to explain the effects of migraine in the brain says Dr Richard Butt, the scientist leading Pfizer's migraine research in Sandwich.

"Migraine is a complicated disease and its biology is not yet entirely understood," he says. "However, we know that it starts when an area

of the brain becomes hyper-excited following some kind of stimulus and this triggers a wave of activity across the brain that causes the migraine symptoms – visual disturbances, nausea and headache, which can last anywhere from a couple of hours to several days."

Many studies have tried to identify what factors trigger the increased brain activity, from changes in the weather and a gluten intolerance to foodstuffs such as red wine and chocolate. "Sometimes sufferers are able to work out what causes an attack, other times people get migraines without knowing why, however, we know that stress and environmental factors can play a role," says Richard.

In the 1980s, researchers made a major breakthrough in the understanding of the pain associated with migraine headaches, linking it to the blood vessels that surround the brain. From this research emerged a new class of drugs to treat a migraine attack, the triptans, one of which was discovered and developed at Pfizer's Sandwich labs (see *The Birth of a Medicine*, right).



heat

"The triptans have become the most common treatment to relieve the symptoms of ongoing migraine attacks," says Richard. "Sufferers take the medicine when they feel a migraine attack coming on and in many patients they are very effective at stopping the pain associated with the attack."

Despite these new medicines, scientific research continues, with recent data suggesting that small protein molecules called neuropeptides are involved. "Neuropeptides help brain cells to communicate with one another," says Richard. "They are released by the activity in the brain and go on to cause the symptoms of a migraine. One neuropeptide, called calcitonin gene related peptide (CGRP), is of particular interest as it is released by nerves in the brain and causes the CNS to become hyperexcited, which, in turn, causes the symptoms of migraine. CGRP is also involved in regulating the blood vessels that surround the brain, which we know are involved in migraine headache."

Unmet medical need

Whilst effective in controlling the headache of migraine in many patients, the triptan drugs do

not work with everyone, says Richard.

"There is still a great unmet need in the acute treatment of migraine, particularly for those patients who do not gain relief from triptans. There is also a small group of patients who suffer frequent migraine attack, experiencing between 2 and 10 attacks per month. Many patients have more 'headache days' than headache-free days and this has a huge impact on their quality of life. This is why we are also looking to develop medicines that prevent migraines from happening in the first place."

The research Richard and his team are carrying out at the labs in Sandwich focuses on several approaches, including gaining a better understanding of the mechanisms in the brain that cause and mediate migraine as well as focusing on the biology of the neuropeptide CGRP in the hope of creating potential new treatments.

"There is a great deal of interest in migraine in academic laboratories at universities and inside pharmaceutical companies so I am very hopeful that we will see more advances over the coming years and, hopefully, better, more effective treatments for migraine patients," says Richard. ■

! The birth of a medicine

In the 1980s, researchers at pharmaceutical company Glaxo Laboratories discovered a new medicine to treat migraine called sumatriptan, the first in what was to become an entire class of medicines, the triptans.

The discovery sparked huge interest among scientists, with many racing to discover their own triptan medicine in order to offer migraine patients greater choice of treatment. A small team of researchers at Pfizer's laboratories in Sandwich did just that, eventually discovering and developing a new medicine for migraine called eletriptan.

Dr Paul Gupta was a member of the team. "About 20 years ago, we started a highly focused project to develop a medicine that would offer patients as much relief from their migraine symptoms as possible," says Paul. "We set out with three very specific goals."

The first goal was to develop a medicine that was absorbed as quickly as possible when given as an oral tablet. "Many migraine sufferers get little warning that they are having a migraine attack and the pain can be unbearable," says Paul. "We set out to create a medicine that got into their system rapidly and started working as quickly as possible."

The second goal was a real challenge, says Paul. "Triptans work by acting on blood vessels surrounding the brain, but the problem was that there was the chance they could also have an effect on blood vessels in other parts of the body," he says. "Some patients were already reporting side effects such as chest tightness as a result of this so, to overcome the problem, we worked hard to design our triptan to have a greater effect on cranial blood vessels and a lesser effect on coronary blood vessels."

The final goal was to create a medicine that had a long duration of action. "A long action in the body is very important as many patients experience migraine attacks that can last for several days and we wanted to keep them pain-free for as long as possible," he says.

Working in a 'hot' area of scientific research was quite an experience, says Paul. "It was very exciting as we were at the forefront of science. When sumatriptan came along the whole area exploded with huge amounts of activity from teams around the world. It was fantastic to be a part of Pfizer's team and to produce a drug at the end of it that we were all very proud of."